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16 October 2003

Åse Damm

PATENT- OG VAREMÆRKESTYRELSEN

# NOVEL THIADIAZOL DERIVATIVES, THEIR PREPARATION AND USE

Modtaget

11 NOV. 2002

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## TECHNICAL FIELD

This invention relates to novel 1,3,4-thiadiazol-2-yl-1,4-diazabicyclo[3.2.2]nonane derivatives and their use in the manufacture of pharmaceutical compositions. The compounds of the invention are found to be cholinergic ligands at the nicotinic acetylcholine receptors and modulators of the monoamine receptors and transporters.

Due to their pharmacological profile the compounds of the invention may be useful for the treatment of diseases or disorders as diverse as those related to the cholinergic system of the central nervous system (CNS), the peripheral nervous system (PNS), diseases or disorders related to smooth muscle contraction, endocrine diseases or disorders, diseases or disorders related to neuro-degeneration, diseases or disorders related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.

## BACKGROUND ART

The endogenous cholinergic neurotransmitter, acetylcholine, exert its biological effect via two types of cholinergic receptors, the muscarinic Acetyl Choline Receptors (mAChR) and the nicotinic Acetyl Choline Receptors (nAChR).

As it is well established that muscarinic acetylcholine receptors dominate quantitatively over nicotinic acetylcholine receptors in the brain area important to memory and cognition, and much research aimed at the development of agents for the treatment of memory related disorders have focused on the synthesis of muscarinic acetylcholine receptor modulators.

Recently, however, an interest in the development of nAChR modulators has emerged. Several diseases are associated with degeneration of the cholinergic system i.e. senile dementia of the Alzheimer type, vascular dementia and cognitive impairment due to the organic brain damage disease related directly to alcoholism. Indeed several CNS disorders can be attributed to a cholinergic deficiency, a dopaminergic deficiency, an adrenergic deficiency or a serotonergic deficiency.

## SUMMARY OF THE INVENTION

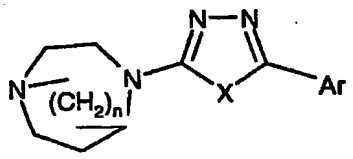
The present invention is devoted to the provision novel modulators of the nicotinic and/or of the monoamine receptors, which modulators are useful for the

treatment of diseases or disorders related to the cholinergic receptors, and in particular the nicotinic acetylcholine receptor (nAChR), the monoamine receptors 5-HTR, DAR and NER, and the biogenic amine transporters for 5-HT, DA and NE.

Due to their pharmacological profile the compounds of the invention may be useful for the treatment of diseases or disorders as diverse as those related to the cholinergic system of the central nervous system (CNS), the peripheral nervous system (PNS), diseases or disorders related to smooth muscle contraction, endocrine diseases or disorders, diseases or disorders related to neuro-degeneration, diseases or disorders related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.

The compounds of the invention may also be useful as diagnostic tools or monitoring agents in various diagnostic methods, and in particular for *in vivo* receptor imaging (neuroimaging), and they may be used in labelled or unlabelled form.

In its first aspect the invention provides novel chemical substances represented by the general Formula I:




(I)

any of its enantiomers or any mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an N-oxide thereof, wherein n is 1, 2 or 3; X represents O, S or Se; and Ar represents a carbocyclic aromatic (aryl) group, or a heterocyclic aromatic (heteroaryl) group, which aromatic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, alkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halogen, $CF_3$, CN, $NO_2$, $NH_2$, carboxy, carbamoyl, amido and sulfamoyl.

In a second aspect the invention provides pharmaceutical compositions comprising a therapeutically effective amount of a compound of the invention, an enantiomer or a mixture of enantiomers, or a pharmaceutically-acceptable addition salt thereof, together with at least one pharmaceutically-acceptable carrier or diluent.

Viewed from another aspect, the invention relates to the use of a compound of the invention, or an enantiomer or a mixture of enantiomers, or a pharmaceutically-acceptable addition salt thereof, for manufacture of a medicament for the treatment, prevention or alleviation of a disease or a disorder or a condition which is responsive to modulation of cholinergic receptors and/or monoamine receptors.

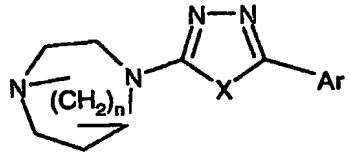
In yet another aspect the invention provides a method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disease or disorder is responsive to modulation of

cholinergic receptors and/or monoamine receptors, which method comprises the step of administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of a compound of the invention, any of its enantiomers or any mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof.

Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

## DETAILED DISCLOSURE OF THE INVENTION

In its first aspect the present invention provides novel chemical substances represented by the general Formula I



(I)

any of its enantiomers or any mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an N-oxide thereof,

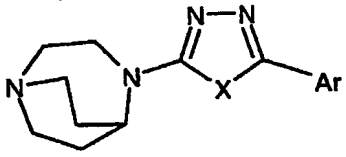
wherein

n is 1, 2 or 3;

X represents O, S or Se; and

Ar represents a carbocyclic aromatic (aryl) group, or a heterocyclic aromatic (heteroaryl) group, which aromatic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, alkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halogen, $CF_3$, CN, $NO_2$, $NH_2$, carboxy, carbamoyl, amido and sulfamoyl.

In a preferred embodiment, where n is 2, the present invention provides novel chemical substances represented by the general Formula II



(II)

wherein X and Ar are as defined above.

In a more preferred embodiment the carbocyclic aromatic (aryl) group is phenyl, indenyl, naphthyl, azulenyl, fluorenyl, or anthracenyl.

In a further preferred embodiment the carbocyclic aromatic group is phenyl, optionally substituted one or two times with substituents selected from the group

consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, cycloalkoxy, halogen, $CF_3$, CN, $NO_2$, $NH_2$, carboxy, carbamoyl, amido and sulfamoyl.

In a most preferred embodiment the compound of the invention is 4-(5-phenyl-1,3,4-thiadiazol-2-yl)-1,4-diazabicyclo[3.2.2]nonane; or an enantiomer or a mixture of enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an N-oxide thereof.

In another preferred embodiment the heterocyclic aromatic (heteroaryl) group is an aromatic monocyclic heterocyclic group, or an aromatic bi- or poly-heterocyclic heterocyclic group, which heterocyclic groups include benzo-fused 5- and 6-membered heterocyclic rings containing one or more heteroatoms, selected from nitrogen (N), oxygen (O), sulphur (S) and/or selen (Se).

In a more preferred embodiment the aromatic monocyclic heterocyclic group is an aromatic 5- or 6-membered heterocyclic monocyclic group.

In an even more preferred embodiment the aromatic monocyclic heterocyclic group is furanyl, in particular 2- or 3-furanyl; thienyl, in particular 2- or 3-thienyl; selenophenyl, in particular 2- or 3-selenophenyl; pyrrolyl (azolyl), in particular 2 or 3-pyrrolyl; oxazolyl, in particular oxazol-2,4 or 5-yl; thiazolyl, in particular thiazol-2,4 or 5-yl; imidazolyl, in particular 2 or 4-imidazolyl; pyrazolyl, in particular 3 or 4-pyrazolyl; isoxazolyl, in particular isoxazol-3,4 or 5-yl; isothiazolyl, in particular isothiazol-3,4 or 5-yl; oxadiazolyl, in particular 1,2,3-oxadiazol-4 or 5-yl, or 1,3,4-oxadiazol-2-yl; triazolyl, in particular 1,2,3-triazol-4-yl or 1,2,4-triazol-3-yl; thiadiazolyl, in particular 1,2,3-thiadiazol-4 or 5-yl, or 1,3,4-thiadiazol-2-yl; pyridinyl, in particular 2,3 or 4-pyridinyl; pyridazinyl, in particular 3 or 4-pyridazinyl; pyrimidinyl, in particular 2,4 or 5-pyrimidinyl; pyrazinyl, in particular 2 or 3-pyrazinyl; and triazinyl, in particular 1,2,4- or 1,3,5-triazinyl.

In yet another preferred embodiment the bicyclic aromatic heterocyclic group is indolyl, in particular 2 or 3-indolyl; isoindolyl, in particular 1 or 3-isoindolyl; benzo[b]furanyl, in particular 2 or 3-benzo[b]furanyl; benzo[b]thienyl, in particular 2 or 3-benzo[b]thienyl; benzoimidazolyl, in particular 2-benzoimidazolyl; benzothiazolyl, in particular 2-benzothiazolyl; quinolinyl, in particular 2,3 or 4-quinolinyl; isoquinolinyl, in particular 1,3 or 4-isoquinolinyl; cinnolinyl, in particular 3 or 4-cinnolinyl; phthalazinyl, in particular 1 or 4-phthalazinyl; quinazolinyl, in particular 2 or 4-quinazolinyl; quinoxalinyl, in particular 2 or 3-quinoxalinyl.

In a still more preferred embodiment the polycyclic aromatic heterocyclic group is a tricyclic heteroaryl groups, in particular 2,3,6 or 7-acridinyl; carbazolyl, in particular 2,3,6 or 7-carbazolyl; phenazinyl, in particular 2,3,7 or 8-phenazinyl; phenothiazinyl, in particular 2,3,7 or 8-phenothiazinyl; and phenoxazinyl, in particular 2,3,7 or 8-phenoxazinyl.

Any combination of two or more of the embodiments described herein is considered within the scope of the present invention.

Definition of Substituents

In the context of this invention an alkyl group designates a univalent saturated, straight or branched hydrocarbon chain. The hydrocarbon chain preferably contain of from one to eighteen carbon atoms ($C_{1-18}$-alkyl), more preferred of from one to six carbon atoms ($C_{1-6}$-alkyl; lower alkyl), including pentyl, isopentyl, neopentyl, tertiary pentyl, hexyl and isohexyl. In a preferred embodiment alkyl represents a $C_{1-4}$-alkyl group, including butyl, isobutyl, secondary butyl, and tertiary butyl. In another preferred embodiment of this invention alkyl represents a $C_{1-3}$-alkyl group, which may in particular be methyl, ethyl, propyl or isopropyl.

In the context of this invention a cycloalkyl group designates a cyclic alkyl group, preferably containing of from three to seven carbon atoms ($C_{3-7}$-cycloalkyl), including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

In the context of this invention a cycloalkyl-alkyl group designates a cycloalkyl group as defined above, which cycloalkyl group is substituted on an alkyl group as also defined above. Examples of preferred cycloalkyl-alkyl groups of the invention include cyclopropylmethyl and cyclopropylethyl.

In the context of this invention an alkenyl group designates a carbon chain containing one or more double bonds, including di-enes, tri-enes and poly-enes. In a preferred embodiment the alkenyl group of the invention comprises of from two to eight carbon atoms ($C_{2-8}$-alkenyl), more preferred of from two to six carbon atoms ($C_{2-6}$-alkenyl), including at least one double bond. In a most preferred embodiment the alkenyl group of the invention is ethenyl; 1- or 2-propenyl (allyl); 1-, 2- or 3-butenyl, or 1,3-butdienyl; 1-, 2-, 3-, 4- or 5-hexenyl, or 1,3-hexdienyl, or 1,3,5-hextrienyl; 1-, 2-, 3-, 4-, 5-, 6-, or 7-octenyl, or 1,3-octdienyl, or 1,3,5-octtrienyl, or 1,3,5,7-octtetraenyl.

In the context of this invention an alkynyl group designates a carbon chain containing one or more triple bonds, including di-ynes, tri-ynes and poly-ynes. In a preferred embodiment the alkynyl group of the invention comprises of from two to eight carbon atoms ($C_{2-8}$-alkynyl), more preferred of rom two to six carbon atoms ($C_{2-6}$-alkynyl), including at least one triple bond. In its most preferred embodiment the alkynyl group of the invention is ethynyl; 1-, or 2-propynyl; 1-, 2-, or 3-butynyl, or 1,3-butdiynyl; 1-, 2-, 3-, 4-pentynyl, or 1,3-pentdiynyl; 1-, 2-, 3-, 4-, or 5-henynyl, or 1,3-hexdiynyl or 1,3,5-hextriynyl; 1-, 2-, 3-, 4-, 5- or 6-heptynyl, or 1,3-heptdiynyl, or 1,3,5-hepttriynyl; 1-, 2-, 3-, 4-, 5-, 6- or 7-octynyl, or 1,3-octdiynyl, or 1,3,5-octtriynyl, or 1,3,5,7-octtetraynyl.

In the context of this invention an alkoxy group designates an "alkyl-O-" group, wherein alkyl is as defined above. Examples of preferred alkoxy groups of the invention include methoxy and ethoxy.

In the context of this invention an alkoxy-alkyl group designates an "alkyl-O-alkyl-" group, wherein alkyl is as defined above. Examples of preferred alkoxy-alkyl groups of the invention include methoxy-methyl, methoxy-ethyl, ethoxy-methyl, and ethoxy-ethyl.

In the context of this invention an alkoxy-alkoxy group designates an "alkyl-O-alkyl-O-" group, wherein alkyl is as defined above. Examples of preferred alkoxy-alkoxy groups of the invention include methoxy-methoxy, methoxy-ethoxy, ethoxy-methoxy, and ethoxy-ethoxy.

In the context of this invention a cycloalkoxy group designates a "cycloalkyl-O-" group, wherein cycloalkyl is as defined above.

In the context of this invention a cycloalkoxy-alkyl group designates a "cycloalkyl-O-alkyl" group, wherein cycloalkyl and alkyl are as defined above.

In the context of this invention a cycloalkoxy-alkoxy group designates a "cycloalkyl-O-alkyl-O-" group, wherein cycloalkyl and alkyl are as defined above.

In the context of this invention halogen represents a fluorine, a chlorine, a bromine or an iodine atom. Thus, a trihalogenmethyl group represents e.g. a trifluoromethyl group, a trichloromethyl group and similar trihalogen-substituted methyl groups.

In the context of this invention an acyl group designates a carboxy group (-COOH) or an alkyl-carbonyl group (alkyl-CO-), wherein alkyl is as defined above. Examples of preferred acyl groups of the invention include carboxy, acetyl, and propionyl.

Pharmaceutically Acceptable Salts

The chemical compound of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention.

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride derived from hydrochloric acid, the hydrobromide derived from hydrobromic acid, the nitrate derived from nitric acid, the perchlorate derived from perchloric acid, the phosphate derived from phosphoric acid, the sulphate derived from sulphuric acid, the formate derived from formic acid, the acetate derived from acetic acid, the aconate derived from aconitic acid, the ascorbate derived from ascorbic acid, the benzenesulphonate derived from benzensulphonic acid, the benzoate derived from

benzoic acid, the cinnamate derived from cinnamic acid, the citrate derived from citric acid, the embonate derived from embonic acid, the enantate derived from enanthic acid, the fumarate derived from fumaric acid, the glutamate derived from glutamic acid, the glycolate derived from glycolic acid, the lactate derived from lactic acid, the maleate derived from maleic acid, the malonate derived from malonic acid, the mandelate derived from mandelic acid, the methanesulphonate derived from methane sulphonic acid, the naphthalene-2-sulphonate derived from naphtalene-2-sulphonic acid, the phthalate derived from phthalic acid, the salicylate derived from salicylic acid, the sorbate derived from sorbic acid, the stearate derived from stearic acid, the succinate derived from succinic acid, the tartrate derived from tartaric acid, the toluene-p-sulphonate derived from p-toluene sulphonic acid, and the like. Such salts may be formed by procedures well known and described in the art.

Other acids such as oxalic acid, which may not be considered pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining a chemical compound of the invention and its pharmaceutically acceptable acid addition salt.

Metal salts of a chemical compound of the invention include alkali metal salts such as the sodium salt of a chemical compound of the invention containing a carboxy group.

In the context of this invention the "onium salts" of N-containing compounds are also contemplated as pharmaceutically acceptable salts. Preferred "onium salts" include the alkyl-onium salts, in particular the methyl-onium salt, the cycloalkyl-onium salts, and the cycloalkylalkyl-onium salts.

Steric Isomers

The chemical compounds of the present invention may exist in (+) and (-) forms as well as in racemic forms (±). The racemates of these isomers and the individual isomers themselves are within the scope of the present invention.

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the diastereomeric salts is by use of an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example.

The chemical compounds of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the chemical compounds of the present invention with an optically active activated carboxylic acid such as that derived

from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the chemical compound of the present invention with an optically active chloroformate or the like.

Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by *Jaques J, Collet A, & Wilen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optical active compounds can also be prepared from optical active starting materials.

**Methods of Preparation**

The chemical substances of the invention may be prepared by conventional methods for chemical synthesis, e.g. those described in the working examples. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods from commercially available chemicals.

Also one compound of the invention can be converted to another compound of the invention using conventional methods.

The end products of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.

**Biological Activity**

The present invention relates to novel chemical substances, which are found to be cholinergic ligands at the nicotinic acetylcholine receptors (nAChR), and modulators of the monoamine receptors, in particular the biogenic amine transporters 5-HT, DA and NE. Also preferred compounds of the invention show selective $\alpha 7$ activity.

In the context of this invention the term "modulator" covers agonists, partial agonists, antagonists and allosteric modulators of the receptor.

Due to their pharmacological profile the compounds of the invention may be useful for the treatment of diseases or conditions as diverse as CNS related diseases, PNS related diseases, diseases related to smooth muscle contraction, endocrine disorders, diseases related to neuro-degeneration, diseases related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.

In a preferred embodiment the compounds of the invention are used for the treatment of diseases, disorders, or conditions relating to the central nervous system. Such diseases or disorders includes anxiety, cognitive disorders, learning deficit, memory deficits and dysfunction, Alzheimer's disease, attention deficit, attention deficit

hyperactivity disorder, Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, Gilles de la Tourette's syndrome, depression, mania, manic depression, schizophrenia, obsessive compulsive disorders (OCD), panic disorders, eating disorders such as anorexia nervosa, bulimia and obesity, narcolepsy, nociception, AIDS-dementia, senile dementia, periferic neuropathy, autism, dyslexia, tardive dyskinesia, hyperkinesia, epilepsy, bulimia, post-traumatic syndrome, social phobia, sleeping disorders, pseudodementia, Ganser's syndrome, pre-menstrual syndrome, late luteal phase syndrome, chronic fatigue syndrome, mutism, trichotillomania, and jet-lag.

In another preferred embodiment the compounds of the invention may be useful for the treatment of diseases, disorders, or conditions associated with smooth muscle contractions, including convulsive disorders, angina pectoris, premature labour, convulsions, diarrhoea, asthma, epilepsy, tardive dyskinesia, hyperkinesia, premature ejaculation, and erectile difficulty.

In yet another preferred embodiment the compounds of the invention may be useful for the treatment of endocrine disorders, such as thyrotoxicosis, pheochromocytoma, hypertension and arrhythmias.

In still another preferred embodiment the compounds of the invention may be useful for the treatment of neurodegenerative disorders, including transient anoxia and induced neuro-degeneration.

In even another preferred embodiment the compounds of the invention may be useful for the treatment of inflammatory diseases, disorders, or conditions, including inflammatory skin disorders such as acne and rosacea, Chron's disease, inflammatory bowel disease, ulcerative colitis, and diarrhoea.

In still another preferred embodiment the compounds of the invention may be useful for the treatment of mild, moderate or even severe pain of acute, chronic or recurrent character, as well as pain caused by migraine, postoperative pain, and phantom limb pain.

Finally the compounds of the invention may be useful for the treatment of withdrawal symptoms caused by termination of use of addictive substances. Such addictive substances include nicotine containing products such as tobacco, opioids such as heroin, cocaine and morphine, benzodiazepines and benzodiazepine-like drugs, and alcohol. Withdrawal from addictive substances is in general a traumatic experience characterised by anxiety and frustration, anger, anxiety, difficulties in concentrating, restlessness, decreased heart rate and increased appetite and weight gain.

In this context "treatment" covers treatment, prevention, prophylactics and alleviation of withdrawal symptoms and abstinence as well as treatment resulting in a voluntary diminished intake of the addictive substance.

In another aspect, the compounds of the invention are used as diagnostic agents, e.g. for the identification and localisation of nicotinic receptors in various tissues.

**Pharmaceutical Compositions**

In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of the chemical substance of the invention.

While a chemical compound of the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising the chemical substance of the invention, or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers therefore, and, optionally, other therapeutic and/or prophylactic ingredients, know and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

The pharmaceutical composition of the invention may be administered by any convenient route, which suits the desired therapy. Preferred routes of administration include oral administration, in particular in tablet, in capsule, in dragé, in powder, or in liquid form, and parenteral administration, in particular cutaneous, subcutaneous, intramuscular, or intravenous injection. The pharmaceutical composition of the invention can be manufactured by any skilled person by use of standard methods and conventional techniques appropriate to the desired formulation. When desired, compositions adapted to give sustained release of the active ingredient may be employed.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

The actual dosage depend on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient per individual dose, preferably of from about 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments.

The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 µg/kg i.v. and 1 µg/kg p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 µg/kg to about 10 mg/kg/day i.v., and from about 1 µg/kg to about 100 mg/kg/day p.o.

**Methods of Therapy**

The chemical substances of the present invention are valuable nicotinic and monoamine receptor modulators, and therefore useful for the treatment of a range of ailments involving cholinergic dysfunction as well as a range of disorders responsive to the action of nAChR modulators.

In another aspect the invention provides a method for the treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disease, disorder or condition is responsive to modulation of cholinergic receptors and/or monoamine receptors, and which method comprises administering to such a living animal body, including a human, in need thereof an effective amount of a compound of the invention.

In a preferred embodiment, the disease, disorder or condition relates to the central nervous system.

In a preferred embodiment, the disease, disorder or condition is anxiety, cognitive disorders, learning deficit, memory deficits and dysfunction, Alzheimer's disease, attention deficit, attention deficit hyperactivity disorder, Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, Gilles de la Tourette's syndrome, depression, mania, manic depression, schizophrenia, obsessive compulsive disorders (OCD), panic disorders, eating disorders such as anorexia nervosa, bulimia and obesity, narcolepsy, nociception, AIDS-dementia, senile dementia, periferic neuropathy, autism, dyslexia, tardive dyskinesia, hyperkinesia, epilepsy, bulimia, post-traumatic syndrome, social phobia, sleeping disorders, pseudodementia, Ganser's syndrome, pre-menstrual syndrome, late luteal phase syndrome, chronic fatigue syndrome, mutism, trichotillomania, and jet-lag.

In a another preferred embodiment, the disease, disorder or condition are associated with smooth muscle contractions, including convulsive disorders, angina pectoris, premature labour, convulsions, diarrhoea, asthma, epilepsy, tardive dyskinesia, hyperkinesia, premature ejaculation, and erectile difficulty.

In a third preferred embodiment, the disease, disorder or condition is related to the endocrine system, such as thyrotoxicosis, pheochromocytoma, hypertension and arrhythmias.

In a fourth preferred embodiment, the disease, disorder or condition is a neurodegenerative disorders, including transient anoxia and induced neurodegeneration.

In a fifth preferred embodiment, the disease, disorder or condition is an inflammatory disorder, including inflammatory skin disorders such as acne and rosacea, Chron's disease, inflammatory bowel disease, ulcerative colitis, and diarrhoea.

In a sixth preferred embodiment, the disease, disorder or condition is mild, moderate or even severe pain of acute, chronic or recurrent character, as well as pain caused by migraine, postoperative pain, and phantom limb pain.

In a seventh preferred embodiment, the disease, disorder or condition is associated with withdrawal symptoms caused by termination of use of addictive substances, including nicotine containing products such as tobacco, opioids such as heroin, cocaine and morphine, benzodiazepines and benzodiazepine-like drugs, and alcohol.

It is at present contemplated that suitable dosage ranges are 0.1 to 1000 milligrams daily, 10-500 milligrams daily, and especially 30-100 milligrams daily, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.005 mg/kg i.v. and 0.01 mg/kg p.o. The upper limit of the dosage range is about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.001 to about 1 mg/kg i.v. and from about 0.1 to about 10 mg/kg p.o.

## EXAMPLES

The invention is further illustrated with reference to the following examples, which are not intended to be in any way limiting to the scope of the invention as claimed.

**Example 1**

**Preparatory Example**

All reactions involving air sensitive reagents or intermediates were performed under nitrogen and in anhydrous solvents. Magnesium sulfate was used as drying agent in the workup-procedures and solvents were evaporated under reduced pressure.

1,4-Diazabicyclo[3.2.2]nonane (Intermediate compound) was prepared according to J. Med. Chem. 1993, 36, 2311-2320.

2-Chloro-5-phenyl-1,3,4-thiadiazole (Intermediate compound)

2-Amino-5-phenyl-1,3,4-thiadiazole sulfate (25.12 g, 142 mmol) was stirred in concentrated hydrochloric acid (300 ml) at 0 °C. Sodium nitrite (12.7 g, 184 mmol) was added during a period of 10 min. The reaction mixture was stirred at 50 °C for 15 h. The hydrochloric acid was evaporated. Aqueous sodium hydroxide (4 M, 250 ml) was added and the the precipitate was filtered. Chromatography on silica gel with ethyl acetate as solvent gave a pure product. Yield 15.5 g (56 %).

4-(5-Phenyl-1,3,4-thiadiazol-2-yl)-1,4-diazabicyclo[3.2.2]nonane fumaric acid salt (Compound 1A):

A mixture of 1,4-diazabicyclo[3.2.2]nonane (1.28 g, 10.2 mmol), 2-chloro-5-phenyl-1,3,4-thiadiazole (2.00 g, 10.2 mmol), triethylamine (2.83 ml, 20.3 mmol) and dioxane (20 ml) was stirred at reflux for 70 h. Aqueous sodium hydroxide (1 M, 25 ml) was added and the mixture was extracted twice with ethyl acetate (2 x 20 ml). Chromatography on silica gel with dichloromethane, 10 % methanol and 1 % aqueous ammonia as solvent gave the title compound as an oil. The corresponding salt was obtained by addition of a diethyl ether and methanol mixture (9:1) saturated with fumaric acid. Yield 0.95 g, 23 %. Mp 150.9°C.

**Example 2**

***In vitro* Inhibition of $^3$H-α-Bungarotoxine Binding in Rat Brain**

In this example the affinity of the compounds of the invention for binding to $\alpha_7$-subtype of nicotinic receptors is determined.

α-Bungarotoxine is a peptide isolated from the venom of the Elapidae snake *Bungarus multicinctus*. It has high affinity for neuronal and neuromuscular nicotinic receptors, where it acts as a potent antagonist.

$^3$H-α-Bungarotoxine labels nicotinic acetylcholine receptors formed by the $\alpha_7$ subunit isoform found in brain and the $\alpha_1$ isoform in the neuromuscular junction.

Tissue preparation

Preparations are performed at 0-4°C. Cerebral cortices from male Wistar rats (150-250 g) are homogenised for 10 seconds in 15 ml of 20 mM Hepes buffer containing 118 mM NaCl, 4.8 mM KCl, 1.2 mM $MgSO_4$ and 2.5 mM $CaCl_2$ (pH 7.5) using an Ultra-Turrax homogeniser. The tissue suspension is subjected to centrifugation at 27,000 x g for 10 minutes. The supernatant is discarded and the pellet is washed twice by centrifugation at 27,000 x g for 10 minutes in 20 ml of fresh

buffer, and the final pellet is then re-suspended in fresh buffer containing 0.01% BSA (35 ml per g of original tissue) and used for binding assays.

Assay

Aliquots of 500 µl of homogenate are added to 25 µl of test solution and 25 µl of $^3$H-α-bungarotoxine (2 nM, final concentration) and mixed and incubated for 2 hours at 37°C. Non-specific binding is determined using (-)-nicotine (1 mM, final concentration). After incubation, the samples are added 5 ml of ice-cold Hepes buffer containing 0.05% PEI and poured directly onto Whatman GF/C glass fibre filters (presoaked in 0.1% PEI for at least 6 hours) under suction, and immediately washed with 2 x 5 ml ice-cold buffer.

The amount of radioactivity on the filters is determined by conventional liquid scintillation counting. Specific binding is total binding minus non-specific binding.

The test value is given as an $IC_{50}$ (the concentration of the test substance which inhibits the specific binding of $^3$H-α-bungarotoxin by 50%).

The results of these experiments are presented in Table 1 below.

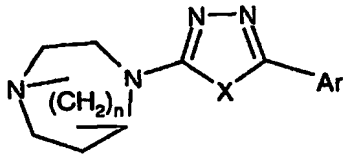
Table 1

Inhibition of $^3$H-α-Bungarotoxine Binding

| Compound No. | $IC_{50}$ (µM) |
|---|---|
| Compound 1A | 0.0067 |

## CLAIMS

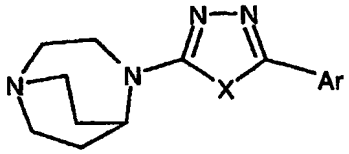
1. A compound represented by Formula I:



(I)

any of its enantiomers or any mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an N-oxide thereof,
wherein
n is 1, 2 or 3;
X represents O, S or Se; and
Ar represents a carbocyclic aromatic (aryl) group, or a heterocyclic aromatic (heteroaryl) group, which aromatic group may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, alkynyl, alkoxy, alkoxy-alkyl, alkoxy-alkoxy, cycloalkoxy, cycloalkoxy-alkyl, cycloalkoxy-alkoxy, halogen, $CF_3$, CN, $NO_2$, $NH_2$, carboxy, carbamoyl, amido and sulfamoyl.

2. The compound of claim 1, represented by Formula II



(II)

wherein
X and Ar are as defined in claim 1.

3. The compound of either of claims 1-2, wherein the carbocyclic aromatic (aryl) group is phenyl, indenyl, naphthyl, azulenyl, fluorenyl, or anthracenyl.

4. The compound of claim 3, wherein the carbocyclic aromatic group is phenyl, optionally substituted one or two times with substituents selected from the group consisting of alkyl, cycloalkyl, cycloalkyl-alkyl, alkoxy, cycloalkoxy, halogen, $CF_3$, CN, $NO_2$, $NH_2$, carboxy, carbamoyl, amido and sulfamoyl.

5. The compound of claim 4, which is 4-(5-phenyl-1,3,4-thiadiazol-2-yl)-1,4-diazabicyclo[3.2.2]nonane; or an enantiomer or a mixture of enantiomers, or a pharmaceutically-acceptable addition salt thereof, or an N-oxide thereof.

6. The compound of either of claims 1-2, wherein the heterocyclic aromatic (heteroaryl) group is an aromatic monocyclic heterocyclic group, or an aromatic bi- or poly-heterocyclic heterocyclic group, which heterocyclic groups include benzo-fused 5- and 6-membered heterocyclic rings containing one or more heteroatoms, selected from nitrogen (N), oxygen (O), sulphur (S) and/or selen (Se).

7. The compound of claim 6, wherein the aromatic monocyclic heterocyclic group is an aromatic 5- or 6-membered heterocyclic monocyclic group.

8. The compound of claim 7, wherein the aromatic monocyclic heterocyclic group is furanyl, in particular 2- or 3-furanyl; thienyl, in particular 2- or 3-thienyl; selenophenyl, in particular 2- or 3-selenophenyl; pyrrolyl (azolyl), in particular 2 or 3-pyrrolyl; oxazolyl, in particular oxazol-2,4 or 5-yl; thiazolyl, in particular thiazol-2,4 or 5-yl; imidazolyl, in particular 2 or 4-imidazolyl; pyrazolyl, in particular 3 or 4-pyrazolyl; isoxazolyl, in particular isoxazol-3,4 or 5-yl; isothiazolyl, in particular isothiazol-3,4 or 5-yl; oxadiazolyl, in particular 1,2,3-oxadiazol-4 or 5-yl, or 1,3,4-oxadiazol-2-yl; triazolyl, in particular 1,2,3-triazol-4-yl or 1,2,4-triazol-3-yl; thiadiazolyl, in particular 1,2,3-thiadiazol-4 or 5-yl, or 1,3,4-thiadiazol-2-yl; pyridinyl, in particular 2,3 or 4-pyridinyl; pyridazinyl, in particular 3 or 4-pyridazinyl; pyrimidinyl, in particular 2,4 or 5-pyrimidinyl; pyrazinyl, in particular 2 or 3-pyrazinyl; and triazinyl, in particular 1,2,4- or 1,3,5-triazinyl.

9. The compound of claim 6, wherein the bicyclic aromatic heterocyclic group is indolyl, in particular 2 or 3-indolyl; isoindolyl, in particular 1 or 3-isoindolyl; benzo[b]furanyl, in particular 2 or 3-benzo[b]furanyl; benzo[b]thienyl, in particular 2 or 3-benzo[b]thienyl; benzoimidazolyl, in particular 2-benzoimidazolyl; benzothiazolyl, in particular 2-benzothiazolyl; quinolinyl, in particular 2,3 or 4-quinolinyl; isoquinolinyl, in particular 1,3 or 4-isoquinolinyl; cinnolinyl, in particular 3 or 4-cinnolinyl; phthalazinyl, in particular 1 or 4-phthalazinyl; quinazolinyl, in particular 2 or 4-quinazolinyl; quinoxalinyl, in particular 2 or 3-quinoxalinyl.

10. The compound of claim 6, wherein the polycyclic aromatic heterocyclic group is a tricyclic heteroaryl groups, in particular 2,3,6 or 7-acridinyl; carbazolyl, in particular 2,3,6 or 7-carbazolyl; phenazinyl, in particular 2,3,7 or 8-phenazinyl; phenothiazinyl, in particular 2,3,7 or 8-phenothiazinyl; and phenoxazinyl, in particular 2,3,7 or 8-phenoxazinyl.

11. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claims 1-10, any of its enantiomers or any mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, together with at least one pharmaceutically-acceptable carrier or diluent.

12. Use of a compound of any of claims 1-10, any of its enantiomers or any mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, for manufacture of a medicament for the treatment, prevention or alleviation of a disease or a disorder or a condition which is responsive to modulation of cholinergic receptors and/or monoamine receptors.

13. The use according to claim 12, wherein the disease, disorder or condition relates to the central nervous system.

14. The use according to claim 13, wherein the disease, disorder or condition is anxiety, cognitive disorders, learning deficit, memory deficits and dysfunction, Alzheimer's disease, attention deficit, attention deficit hyperactivity disorder, Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, Gilles de la Tourette's syndrome, depression, mania, manic depression, schizophrenia, obsessive compulsive disorders (OCD), panic disorders, eating disorders such as anorexia nervosa, bulimia and obesity, narcolepsy, nociception, AIDS-dementia, senile dementia, periferic neuropathy, autism, dyslexia, tardive dyskinesia, hyperkinesia, epilepsy, bulimia, post-traumatic syndrome, social phobia, sleeping disorders, pseudodementia, Ganser's syndrome, pre-menstrual syndrome, late luteal phase syndrome, chronic fatigue syndrome, mutism, trichotillomania, and jet-lag.

15. The use according to claim 12, wherein the disease, disorder or condition are associated with smooth muscle contractions, including convulsive disorders, angina pectoris, premature labour, convulsions, diarrhoea, asthma, epilepsy, tardive dyskinesia, hyperkinesia, premature ejaculation, and erectile difficulty.

16. The use according to claim 12, wherein the disease, disorder or condition is related to the endocrine system, such as thyrotoxicosis, pheochromocytoma, hypertension and arrhythmias.

17. The use according to claim 12, wherein the disease, disorder or condition is a neurodegenerative disorders, including transient anoxia and induced neuro-degeneration.

18. The use according to claim 12, wherein the disease, disorder or condition is an inflammatory disorder, including inflammatory skin disorders such as acne and rosacea, Chron's disease, inflammatory bowel disease, ulcerative colitis, and diarrhoea.

19. The use according to claim 12, wherein the disease, disorder or condition is mild, moderate or even severe pain of acute, chronic or recurrent character, as well as pain caused by migraine, postoperative pain, and phantom limb pain.

20. The use according to claim 12, wherein the disease, disorder or condition is associated with withdrawal symptoms caused by termination of use of addictive substances, including nicotine containing products such as tobacco, opioids such as heroin, cocaine and morphine, benzodiazepines and benzodiazepine-like drugs, and alcohol.

21. A method of the treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disease or disorder is responsive to modulation of cholinergic receptors and/or monoamine receptors, which method comprises the step of administering to such a living animal body, including a human, in need thereof a therapeutically effective amount of a compound of any of claims 1-10, any of its enantiomers or any mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof.

## ABSTRACT


### NOVEL THIADIAZOL DERIVATIVES, THEIR PREPARATION AND USE

This invention relates to novel 1,3,4-thiadiazol-2-yl-1,4-diazabicyclo[3.2.2]nonane derivatives and their use in the manufacture of pharmaceutical compositions. The novel 1,3,4-thiadiazol-2-yl-1,4-diazabicyclo[3.2.2]nonane derivatives of the invention are found to be cholinergic ligands at the nicotinic acetylcholine receptors and modulators of the monoamine receptors and transporters.

Due to their pharmacological profile the compounds of the invention may be useful for the treatment of diseases or disorders as diverse as those related to the cholinergic system of the central nervous system (CNS), the peripheral nervous system (PNS), diseases or disorders related to smooth muscle contraction, endocrine diseases or disorders, diseases or disorders related to neuro-degeneration, diseases or disorders related to inflammation, pain, and withdrawal symptoms caused by the termination of abuse of chemical substances.

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